

Oxygen therapy for sepsis and prevention of complications

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Patients with sepsis have a wide range of respiratory disorders that can be treated with oxygen therapy. Experimental data in animal sepsis models show that oxygen therapy significantly increases survival, while clinical data on the use of different oxygen therapy protocols are ambiguous. Oxygen therapy, especially hyperbaric oxygenation, in patients with sepsis can aggravate existing oxidative stress and contribute to the development of disseminated intravascular coagulation. The purpose of this article is to compare experimental and clinical data on oxygen therapy in animals and humans, to discuss factors that can influence the results of oxygen therapy for sepsis treatment in humans, and to provide some recommendations for reducing oxidative stress and preventing disseminated intravascular coagulation during oxygen therapy.

Key Words: anticoagulants; antioxidants; oxygen therapy; platelets; sepsis; thrombosis

INTRODUCTION

Sepsis remains a pressing global healthcare concern [1,2]. Moreover, sepsis and septic complications following infection continue to grow worldwide [3,4]. Sepsis and septic shock lead to death in 20%–50% of cases [5,6]. Until the 1990s, the most frequent primary source of sepsis was the abdominal cavity, but in subsequent years, lung infections have become the main reason for the emergence of sepsis [7,8]. Currently, sepsis is most commonly caused by pneumonia; the less frequent causes of sepsis are intra-abdominal infection, primary bacteremia, catheter-inserted infections, urinary tract infections, etc. [9,10]. Moreover, sepsis in pneumonia causes the highest mortality [11]. The bacterial strains that cause sepsis vary over time. Gram-negative organisms have become less common, and gram-positive infections have begun to cause sepsis more frequently [12,13].

Treatment for sepsis includes antibiotics, elimination of infection foci, and maintenance of vital functions and homeostasis [14,15]. Appropriate guidelines, protocols, and clinical recommendations are used for the diagnosis and treatment of sepsis [16–18]. However, they do not contain clear criteria for oxygen therapy [19,20]. At the same time, respiratory disorders in patients with sepsis are overt and have a complex character. The lack of oxygen therapy recommendations seems particularly intriguing given the relatively long history surrounding oxygen in medicine. More than 220 years ago, Thomas Beddoes started to use oxygen for the treatment of asthma, heart disease, and various other illnesses [21], and in 1885, George

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Holtzaple published the results of using oxygen to treat pneumonia and established its role in the treatment of critical conditions [22].

In sepsis, acute pulmonary injury develops in more than 40% of cases, and acute respiratory distress syndrome develops in 35% of patients [23]. Mortality rate due to the latter complication (approximately 45%) has remained relatively unchanged over the past 40 years [23,24]. Respiratory failure is the main cause of multiple organ dysfunction and failure. In critical conditions, there is a correlation between changes in central venous oxygen saturation (ScvO₂; the percentage of oxygen bound to hemoglobin [Hb] in blood returning to the right side of the heart) and the level of tissue hypoxia due to reduced oxygen delivery [23,24]. It is necessary to correct several parameters at once, such as cardiac output, blood Hb count, and arterial blood oxygen saturation, to improve oxygen delivery to tissues. In this case, it is necessary to achieve the target level of 70% ScvO₂ [25]. The complexity of correcting many interrelated parameters of gas metabolism in sepsis leads to ambiguous criteria for sepsis oxygen therapy. The purpose of this article is to compare and contrast experimental and clinical data on oxygen therapy in animals and humans, to discuss factors that can influence the success or failure of oxygen therapy for sepsis (OTS) in humans, and to provide some recommendations to reducing oxidative stress and preventing disseminated intravascular coagulation (DIC) in septic patients during oxygen therapy.

HYPERBARIC OTS IN ANIMALS

Experiments in rats and mice provide most of the experimental evidence regarding the efficacy of OTS in animal models. These experiments use different techniques for provoking sepsis, such as cecum ligation and puncture (CLP) and intra-abdominal pathogen injections [26]. Animal experiments are necessary for many reasons, but the extrapolation of experimental data into clinical practice can be improper [27]. Dissimilarities in interactions between pathogen and host, anatomical and physiological differences, variable human translatability of causative pathogenic sepsis agents, and many other factors are obstacles to the application of animal data in the clinic [28,29]. In most experiments, OTS increases animal survival. In rat models with a mortality rate of 100% without treatment, intermittent hyperbaric oxygen therapy (HBOT; breathing oxygen in a pressurized chamber or tube) reduced the mortality rate to 8% (P<0.005); in a model with a mortality

rate of 79% without treatment, intermittent HBOT reduced the rate to 23% (P<0.005) [30]. It is easier to experimentally demonstrate the effectiveness of HBOT in different experimental models than to establish the optimal HBOT time [31]. Early HBOT (98% oxygen under pressure up to 2.4 atmospheres within 1 hour after CLP) reduces the systemic inflammatory response [32]. The protective role of HBOT in CLP-induced sepsis may be related to the expression of interleukin (IL)-10 by peritoneal macrophages [33]. Other mechanisms describing the positive action of HBOT are also possible [34].

These mechanisms include the “superinduction” of heme oxygenase-1, inhibition of nitric oxide (NO) production and prevention of lung damage caused by lipopolysaccharides, reduction of inflammatory mediators due to HBOT, modulation of nuclear factor-kappa B activity and inhibition of excessive myeloperoxidase production, suppression of bacterial growth in the small intestine, preservation of erythrocyte deformability, and acceleration of free radical acceptor synthesis to mitigate the effects of reactive oxygen species (ROS). Routine use of HBOT in addition to antibiotic therapy may increase survival in sepsis [35]. In addition, ozone therapy is highly effective in increasing animal survival after intraperitoneal pathogen inoculation [36]. HBOT and ozone therapy reduce oxidative stress and myeloperoxidase synthesis, decrease the concentration of tumor necrosis factor (TNF)- α and IL-1 β , and prevent lung damage [36]. In CLP-induced sepsis, the use of 98% O₂ (2.4 atmospheres) provides a 52% survival rate compared to 13% in the control group [32]. The positive effect is represented by a decrease in the expression of TNF- α , IL-6, and IL-10 [32,37]. Thus, most experimental data demonstrates the beneficial effects of oxygen therapy in the treatment of sepsis.

OTS IN HUMANS

Analysis of the data available from Medline, the Cochrane Database of Systematic Reviews, and other sources indicated that different aspects of HBOT optimal use for sepsis treatment need further research [38]. More research is also needed regarding the use of normobaric oxygen (adjuvant oxygenation by nasal cannula or facemask at one atmosphere of pressure), which has the potential to be as effective as the use of antibiotics [39]. Normobaric oxygen should be used immediately after the development of sepsis; otherwise, it will not increase patient survival [40]. At the same time, other aspects of OTS are also important and should also be studied [41]. Data on the partial pressure of oxygen (PaO₂) in arterial blood indicate

that both high and low PaO₂ can increase sepsis mortality [42]. Even though hyperoxia stimulates the production of ROS, HBOT is used to treat sepsis in humans [43-45]. Oxygen therapy reduces mortality by stimulating the anti-inflammatory response and suppressing the pro-inflammatory response [30,46]. Although early HBOT has a positive effect on anti-inflammatory parameters and mortality, it is not known whether delayed oxygen therapy prevents the development of septic shock [47,48]. Delayed HBOT promotes the oxidation of succinate to fumarate in the mitochondria and prevents the accumulation of succinate, which leads to organ damage in sepsis [49]. Although theoretical explanations for the benefits of OTC are numerous, the adequate practical use of oxygen in sepsis does not have precise criteria. An individualized approach is necessary to decrease the risk of oxygen injury to the lungs. Oxygenation of 90% and tolerable hypercapnia are considered acceptable [50].

In contrast, liberal oxygen therapy induces hyperoxemia in most patients and decreases their survival. Mild hyperoxemia decreases oxygen delivery [51]. High oxygen levels in the central venous blood (ScvO₂, 88%–100%) increase mortality in patients with sepsis [52]. High oxygen supplementation (FiO₂>65%) and hypoxemia (PaO₂<7 kPa) can increase in-hospital mortality [53]. Short-term hyperoxia (<7–10 minutes) can cause atelectasis [54]. Providing normoxemia may reduce the negative effects of hyperoxemia in sepsis [55]. HBOT can provoke a depletion of leukocytes and platelets and cause DIC [56]. Although liberal oxygen therapy has been a cornerstone of therapy for sepsis, alertness in hyperoxia necessitates titration of OTS to normoxia [57]. Hyperoxia also increases mortality in patients who achieve normoxia after hospitalization and therefore requires targeting for normoxia after the initiation of mechanical ventilation, which may improve patient outcomes [58]. Hyperoxia can cause damage to the alveoli, pulmonary edema, and a systemic inflammatory response; therefore, targets should be chosen to reduce oxygenation [59,60]. Hyperoxia also changes the composition of surfactant proteins; suppresses mucociliary clearance; causes vasoconstriction; and decreases coronary blood flow, cardiac output, and microvascular perfusion [61]. On the other hand, until now, the idea of “acceptable hypoxemia” has not been tested [62]. But if not corrected, tissue hypoxia can cause multiple organ dysfunction and death. As a result, OTS is performed in many patients even without documented hypoxia. Hypoxia significantly increases mortality, which increases in parallel with PO₂ [63].

Thus, OTS may worsen some situations rather than improve

survival [42,64]. Oxygen is a medicine: it has both the desired positive effects and dangerous side effects. The balance between the positive and negative effects of higher and lower doses of OTS is still unknown [65-67].

OXIDATIVE STRESS IN SEPSIS AND OXYGEN THERAPY

Given that oxygen is a drug, its narrow range of therapeutic efficacy and safety in sepsis should be recognized. The toxic effects of hyperoxia are well known; particularly, high barometric pressure of oxygen (more than two atmospheres) “poisons” the brain, causing the Paul Ebert effect: nausea, blurred vision, coughing, trouble breathing, headache, dizziness, muscle twitching, irritability, disorientation, and convulsions among other effects [68-70]. Although oxygen therapy is recommended for many specific pathologies and clinical situations, for example, necrotizing fasciitis, chronic wounds, diabetic retinopathy, and carbon monoxide poisoning [71-74], the use of oxygen for sepsis requires a cautious approach. Bacteremia is one of the reasons that increased caution should be taken surrounding the use of oxygen in sepsis. Bacteremia complicates OTS because it increases oxidative stress in the blood plasma. The increase in oxidative stress is associated with a mechanism for removing bacterial infection from the bloodstream in humans, the main mechanism for doing so being oxycytosis [75]. This occurs in arterial blood, where red blood cells kill bacteria through the oxygen released by oxyhemoglobin. Usually, the amount of oxygen released is limited by the amount required to kill bacteria, and oxycytosis does not lead to significant oxidation of blood plasma or a decrease in its redox potential [76].

The situation changes with sepsis. The latter is primarily caused by the so-called sepsis-causing bacteria that can survive oxidation. Being resistant to active oxygen and ROS, they provoke red blood cells to release the maximal possible amount of oxygen from oxyhemoglobin (Figure 1). The released oxygen dissolves in the blood plasma. Oxygen therapy, especially HBOT, raises the quantity of dissolved oxygen in the blood plasma [58-61]. The increased concentration of dissolved oxygen causes oxidation of plasma components (proteins, lipids, hormones, amino acids, peptides, vitamins, etc.), depletion of the antioxidant capacity of plasma, and platelet activation [56,76]. Oxidation of plasma components causes disruption of hormonal regulation and homeostasis [77]. Depletion of the antioxidant capacity of plasma causes

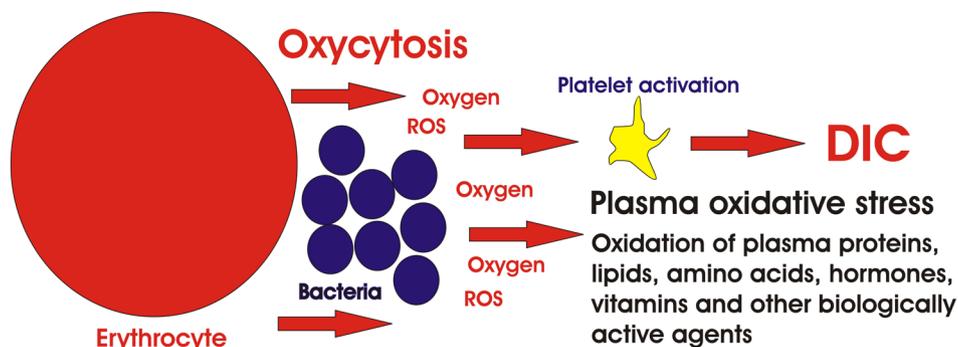


Figure 1. Oxidation of plasma components, platelet activation and depletion of the antioxidant capacity of blood plasma by oxycytosis. ROS: reactive oxygen species; DIC: disseminated intravascular coagulation.

damage to cell membranes and DNA [78]. Oxygen dissolved in blood plasma activates platelets, which can cause DIC after activation by oxygen [79-82]. Activated platelets also generate ROS [83] following glycoprotein (GP) IIb/IIIa receptor stimulation, arachidonic acid metabolism, glutathione (GSH) cycle, phosphoinositide metabolism, etc [84,85]. As a result, ROS generation continues as a chain reaction. Sepsis-causing bacteria penetrate the erythrocyte membranes and cause Hb leakage and hemolysis [77,79]. In turn, intravascular hemolysis activates platelets due to direct activation by Hb, increased ROS, nitrogen oxide (NO) removed by liberated Hb, and the release of intra-erythrocyte adenosine diphosphate [86]. Platelets are also activated by extracellular neutrophil traps, histones, and aggregates of platelets and leukocytes [87-89]. Thrombin also activates platelets. With sepsis, an overproduction of thrombin occurs, which increases inflammation. Thrombin activates platelets via GPIIb and protease-activated receptors PAR1 and PAR4 [90]. Thrombin generation occurs through the fibrin network, extracellular neutrophil traps, and histones [91]; expression of encoded tissue factor, cytokines, and microparticles by endothelial cells [92]; initiation of bacterial polyphosphate via the “contact” pathway [93]; and invasion into endothelium by bacteria and, as a result, platelet activation (via FcγRIIa, αIIbβ3, and platelet factor-4) [94]. During infection, thrombin generation can be stimulated by many other pathways as well [95,96].

Thus, the mechanism of bacteria-killing in the bloodstream by oxygen released from oxyhemoglobin (oxycytosis) demonstrates one of the risks of using oxygen in the treatment of sepsis. Excessive release of oxygen from erythrocytes, together with the use of OTS, can significantly increase the amount of oxygen dissolved in blood plasma. Dissolved oxygen causes

many harmful effects, and one of the most serious complications is platelet activation, which can initiate DIC. Although oxycytosis and OTS alone can cause DIC. Together, they do so more quickly and easily. HBOT for sepsis dissolves more oxygen in the blood than normobaric OTS. Therefore, the use of HBOT in sepsis is more dangerous than that of normobaric OTS.

HENRY'S LAW AND OXYGEN THERAPY IN SEPSIS

HBOT can have unexpected effects on oxygen transport. It is known that blood carries oxygen in two forms: dissolved in plasma and bound to Hb. Dissolved oxygen is not involved in oxygen transfer due to its low solubility. Arterial blood with 100 mm Hg PO_2 dissolves only 0.3 ml of O_2 per 100 ml of blood, while 100 ml of Hb contains 20 ml of oxygen [97]. Dissolved oxygen takes part in oxygen transport when 100% oxygen is inhaled, which typically raises alveolar PO_2 to over 600 mm Hg and increases the concentration of dissolved oxygen from 0.3 to 2 ml in 100 ml of blood. This amount of dissolved oxygen is 40% of the difference in arterial-venous oxygen concentrations of 5 ml O_2 /100 ml of blood [98]. Oxygen dissolves in blood according to Henry's law [99,100]. The law says that the quantity of O_2 dissolved in blood is proportional to PO_2 : $[O_2]=k PO_2$, where $k = (0.003 \text{ ml } O_2/100 \text{ ml of blood})^{-1} \text{ mm Hg}^{-1}$ (Figure 2). The oxygen concentration in arterial blood correlates with the partial pressure of inhaled O_2 , the intensity of ventilation and gas exchange, the level of Hb, and the affinity of Hb for O_2 [101]. At a high partial pressure of inhaled O_2 , the role of dissolved oxygen in O_2 transfer increases, and the role of Hb decreases [102]. At a PaO_2 of more than 2.2 atmospheres, Hb ceases to

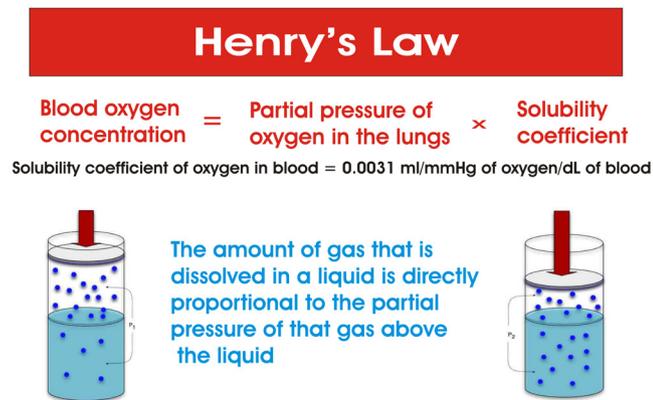


Figure 2. Henry's law and the dissolution of oxygen in blood plasma.

transport oxygen to the tissues, and as a result, tissue respiration is provided by oxygen dissolved in the blood plasma [103]. If the PaO_2 for breathing is three atmospheres, the blood dissolves about 6 vol% oxygen (6 ml of O_2 in 100 ml of plasma), and this amount of oxygen corresponds to the normal oxygen consumption of the human body (arteriovenous oxygen difference) when erythrocytes pass through the capillaries without emitting oxygen and not binding carbon dioxide [102-104]. As a result, a paradoxical situation may develop: the more oxygen the patient breathes under pressure, the less oxygen is delivered to the tissues and the less carbon dioxide is removed from the tissues (Figure 3).

Many publications show that hyperoxia increases sepsis mortality [52-67]. It is difficult to recommend a specific oxygen therapy policy covering all clinical situations, so OTS should be used with caution. In patients with sepsis, along with clinical, instrumental, and laboratory parameters, plasma oxidative stress and blood clotting should also be monitored.

MARKERS OF OXIDATIVE STRESS AND PLATELET ACTIVATION

In sepsis, the markers of oxidative stress indirectly show the intensity of oxygen release by erythrocytes during oxyctosis and the amount of dissolved oxygen in the blood plasma. Oxidative stress can be detected by finding oxidants, such as free radicals; testing the level of antioxidants; measuring oxidation products, including protein carbonyl, F2-isoprostanes, malondialdehyde, and 8-oxo-20-deoxyguanosine (8-OHdG); and measuring the redox balance check (ratio of reduced GSH/oxidized GSH). It is reasonable to test different oxidative

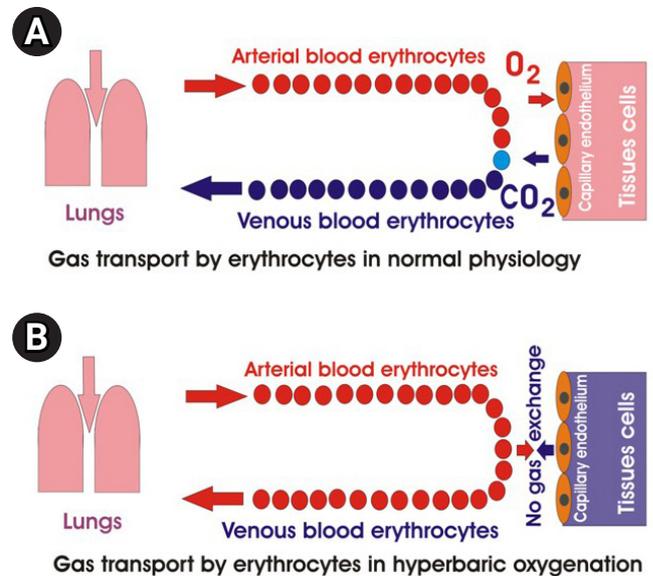


Figure 3. Gas transport by erythrocytes in normal physiology (A) and hyperbaric oxygen therapy (B).

markers simultaneously [105].

In clinical practice, oxidative stress is often detected by separate testing of human serum albumin, plasma proteins, vitamin C, etc. Serum albumin is the main antioxidant against ROS [106]. It contains a cysteine residue (Cys34) that is oxidized by the formation of a disulfide bond with free cysteine amino acids [107]. Oxidative damage to proteins increases the level of carbonylation [108]. This biomarker is formed early and is stable [109]. Carbonyl groups are formed in various ways, for example, by cleavage of the main protein chain, in particular at proline, lysine, and arginine side chains, and by lysine deamination [110]. The most commonly used methods for testing carbonyl groups are enzyme-linked immunosorbent assay and high-performance liquid chromatography HPLC. They are popular due to their high throughput and standardization [111].

The antioxidant system includes superoxide dismutase, GSH peroxidase, catalase, and non-enzymatic antioxidants (ascorbic acid, tocopherols, bilirubin, GSH, etc.). Ascorbic acid (vitamin C) is useful for the evaluation of oxidative stress. It scavenges free radicals, hydroxyl radicals, hydrogen peroxide (H_2O_2), singlet oxygen, and others [112,113]. For the assessment of oxidative stress *in vivo*, new reliable and simple tests have been proposed and adapted for automatic analyzers. These tests allow for fast processing of many samples and avoid manual handling of samples and reagents.

Given that oxidative stress activates platelets and, thus, can

trigger DIC [56,76], antiplatelet therapy for sepsis is imperative. It is necessary to constantly check the condition of blood coagulation, with particular attention to tests for platelet function, for adequate antiplatelet therapy. Numerous tests show platelet function. Monitoring of antiplatelet therapy and diagnosis of platelet dysfunction are necessary to assess the risk of DIC and bleeding [114]. Moreover, markers of platelet activation can help predict sepsis [115].

Born's test, developed in the 1960s, was the first test to diagnose platelet function. Aggregometry of light transmission in platelet-rich plasma reveals platelet aggregation in response to various agents causing aggregation *in vitro* [116]. In the 1980s, other tests of platelet function entered clinical practice, such as *ex vivo* flow cytometry, measurement of nucleotides and platelet-specific compounds, aggregometry of whole blood platelets, etc. [117]. Platelets are also easily activated during blood sampling and blood manipulation [118]. New, simpler, and more reliable platelet function tests are currently being developed. They provide testing of platelet function directly at the point of care or at the patient's bedside and are also becoming available in general laboratories, hospitals, and in everyday practice [119]. Currently, various assays are used to monitor antiplatelet therapy, including the VerifyNow P2Y12 assay, Multiplate analyzer, VASP-P (vasodilator-stimulated phosphoprotein-phosphorylation), PFA-100/200 (platelet function analyzer), and others. They overcame the problems of previous tests, such as Born's aggregometry. Monitoring antiplatelet therapy in OST is necessary to make adequate therapeutic decisions and control the treatment of sepsis [119].

It is important to be aware of the risks of OTS and to predict possible complications before they begin. Some preventive measures to reduce the risk of DIC may be prudent. Before and during oxygen therapy, certain medications may be required to increase the antioxidant potential of blood plasma and to prevent platelet activation and aggregation.

NEUTRALIZATION OF ROS IN PLASMA AND INCREASING THE ANTIOXIDANT POTENTIAL OF PLASMA

Innate immune mechanisms for clearing the bloodstream of bacterial infection include oxycytosis - the destruction of bacteria by oxygen released from erythrocytes [75-77]. The bacteria that cause sepsis are resistant to oxygen, and red blood cells release the maximum amount of oxygen. Excess oxygen depletes the antioxidant capacity of plasma and causes redox

imbalances, in particular, a decrease in GSH levels. GSH provides protection against oxidative stress. It is synthesized from cysteine, glycine, and glutamate [105]. A decrease in plasma GSH activity increases sepsis mortality [106,107]. In plasma, GSH not only traps ROS but also removes toxins and drugs [108]. GSH is also depleted as sepsis progresses to septic shock [109]. To prevent DIC, septic shock, and multiple organ failure (MOF), GSH should be included in sepsis therapy as soon as infection enters the bloodstream and oxycytosis begins. There are currently no tests to detect the early stages of bacteremia and oxycytosis, and GSH therapy should be started in conjunction with antibiotic therapy as soon as sepsis is suspected [105-107]. The chemical structure of synthetic GSH is similar to that of natural GSH produced in the human body, so overdose is rare. GSH is non-toxic; it has very few side effects and interacts weakly with some drugs, such as tetracycline, sulfanilamide, and vitamin B12. Intramuscular injections of GSH (600 mg in 4 ml of 0.9% NaCl) are possible, but intravenous infusions of GSH are preferred. The total dose of GSH depends on the degree of plasma redox potential depletion [106-108]. GSH can be used with several antioxidant vitamins, such as vitamins C, E, and A.

Vitamin C (ascorbic acid) can be used to increase the redox potential of plasma alone or together with GSH and vitamins A and E. As an antioxidant vitamin, ascorbic acid is preferred over vitamin E and vitamin A due to its water solubility and low toxicity. Humans cannot synthesize vitamin C, while other animals rapidly increase their production during oxidative stress [120]. Vitamin C is a neuroprotector, immunomodulator, and cofactor for the synthesis of vasopressors [121]. High doses of vitamin C have been used for many years in complementary and alternative medicine [122]. Vitamin C has a protective effect against oxidative stress in sepsis and septic shock [123]. High doses of vitamin C reduce the degree of multiple organ failure [124]. In a double-blind, randomized clinical trial, 28-day mortality was decreased following vitamin C administration [125,126]. Vitamin C in combination with thiamine and hydrocortisone also significantly reduces sepsis mortality [122]. Some clinicians began using ascorbic acid in their daily practice for the treatment of sepsis before testing for ascorbic acid in clinical trials [127]. Early studies used 1 to 2 g intravenous doses of ascorbic acid every 8 hours. The high dose of ascorbic acid (1,584 mg/kg/day) was also well tolerated [126]. The antioxidant effect of ascorbic acid is dose-dependent and is maximal at plasma concentrations >175 mg/L [128]. Optimal doses for intravenous infusion are approximately 10 g per day

but may be higher [126-128]. High plasma concentrations of ascorbic acid can only be achieved by intravenous infusion, not oral administration [127].

High doses of vitamin C can cause mild renal impairment and glucose-6-phosphate dehydrogenase deficiency. Calcium oxalate nephropathy is a rare, potentially toxic effect of vitamin C. Side effects are dose-dependent, but no adverse clinical reactions have been reported in most patients and healthy volunteers [121-123]. It is possible for ascorbic acid to become a standard component of sepsis therapy as more data are uncovered [128].

There are conflicting publications regarding the use of retinol (vitamin A), tocopherols (vitamin E), and vitamin D in the treatment of sepsis and septic shock [129-138]. The use of these vitamins for sepsis requires further study. Again, it should be noted that antioxidant therapy for the prevention of DIC should be carried out before platelet activation by oxygen and ROS; otherwise, therapy may be less effective or even ineffective.

PREVENTION OF PLATELET AGGREGATION

Neutralizing oxygen and ROS in plasma and increasing plasma redox potential can prevent platelet activation that causes DIC. However, if antioxidant therapy fails and platelet activation occurs, early anticoagulant therapy is indispensable [139]. The state of coagulation must be quickly and repeatedly assessed to identify the initiation of DIC syndrome [140]. Particular attention should be paid to platelets [141,142]. Intensive anticoagulant therapy reduces in-hospital mortality [143]. Antiplatelet medications prevent DIC and reduce mortality or complications in critically ill patients [144-146]. Antiplatelet therapy before hospitalization and early targeted therapy reduces the risk of DIC [147]. In experimental models of sepsis, aspirin or P2Y₁₂ inhibitors prevent organ failure and mortality without increasing bleeding [148]. Platelet formation can be inhibited either by aspirin (acetylsalicylic acid), which suppresses COX-1 activity and blocks the synthesis of thromboxane A₂, or by clopidogrel and ticagrelor, which stop platelet activation induced by adenosine diphosphate [149]. Aspirin is a cheap and relatively safe drug at low doses for platelet inhibition that can effectively reduce mortality from sepsis [150,151]. Aspirin can also be used in low-grade DIC treatment [152]. Low-dose aspirin decreases the need for intensive care [153,154]. A large study of 7,945 intensive care unit (ICU) patients showed the effectiveness of aspirin for increasing sepsis patient survival

[155]. Another study analyzed 886 patients with sepsis and found that aspirin significantly reduced mortality in ICUs and hospitals [156]. On the other hand, a recent study has shown that daily low-dose aspirin treatment did not reduce deaths associated with sepsis in community-dwelling older adults [157].

Clopidogrel and ticagrelor may be alternatives to aspirin to prevent DIC. These antiplatelet drugs may become a new approach to the prevention of DIC and multiple organ failure [158,159]. Ticagrelor inhibits platelet aggregation faster and more efficiently than clopidogrel [160]. The mortality risk is lower with ticagrelor therapy compared with clopidogrel therapy [161]. Ticagrelor also inhibits the reuptake of adenosine. Clopidogrel and other thienopyridines do not affect adenosine metabolism [162].

Heparin can also be used to prevent DIC; it is not an antiplatelet agent. The anticoagulant effect of heparin is determined by the activation of antithrombin III, which inactivates thrombin, activated factor X (factor Xa), and other proteases [163]. Heparin can reduce DIC and MOF [164]. It decreases mortality in sepsis [165]. Improvement of the state of hypercoagulability in sepsis with heparin reduces the incidence of DIC or multiple organ failure and also reduces overall ICU stay [166]. Heparin decreases mortality in sepsis without causing bleeding [167].

DISCUSSION

The results of oxygen therapy in the experimental treatment of sepsis in animal models contradict the results of the use of oxygen in clinical practice. HBOT in experimental sepsis increases survival, reduces oxidative stress, decreases the concentration of TNF- α and IL-1 β , prevents lung damage, and has other positive effects by suppressing the expression of TNF- α , IL-6, and IL-10 [20-27]. In contrast to experimental data, clinical data on the use of oxygen in patients with sepsis are not exactly definitive both regarding hyperbaric and normobaric oxygen. When using normobaric oxygen as part of sepsis treatment, both an increase and a decrease in the mortality rate were recorded [30,40,42,46]. Data on the use of hyperbaric oxygen in sepsis are also inconsistent. Early HBOT may have a positive effect on anti-inflammatory parameters and mortality [47,48], while delayed HBOT can prevent organ damage from sepsis [49].

However, the majority of clinical studies [51-64] demonstrate that HBOT can increase mortality by causing decreased oxygen delivery to tissues; alveolar damage, pulmonary edema, and atelectasis; vasoconstriction, decreased coronary

blood flow, cardiac output, and microvascular perfusion; and DIC. Perhaps the negative effects of hyperbaric oxygenation in sepsis treatment can be partially explained by Henry's law, the presence of additional oxidative stress in sepsis, and a decrease in the redox potential of plasma due to oxycytosis. Thus, neutralizing ROS in plasma and increasing the antioxidant potential of plasma to mitigate some of the negative effects of HBOT through the use of GSH, ascorbic acid, and other antioxidants may be reasonable. As for DIC syndrome, which can be triggered by sepsis and HBOT, early anticoagulant therapy and platelet inactivation seem to be indispensable.

The results of the studies carried out to date on the use of oxygen in the complex therapy of sepsis are contradictory and do not assist the development of effective and safe protocols for the use of oxygen in sepsis treatment; on the other hand, the continuation of research and the further accumulation of statistical data in the form in which it happened before will hardly help the development of adequate protocols for oxygen therapy with respect to sepsis treatment. The only thing that can be more or less confidently asserted from the data accumulated to date is that normobaric OTS is safer than HBOT. An individualized approach to OTS has many nuances, requires a physician's personal experience, and can be difficult to implement in modern conditions of treating patients by a group of doctors. Perhaps new innovative basic theoretical and clinical research is needed to provide a breakthrough in the optimization of OTS and to ensure the development of appropriate optimal protocols.

CONCLUSION

Sepsis causes a wide range of respiratory disorders that require oxygen therapy. The use of oxygen therapy in animal models of sepsis is effective and improves animal survival in the majority of experiments. The use of different protocols for oxygen therapy in patients with sepsis gives less unequivocal results. Oxygen therapy, especially HBOT, increases the concentration of dissolved oxygen in plasma, depletes plasma antioxidant potential, suppresses oxygen transport by erythrocytes, decreases carbon dioxide removal from the tissues, activates platelets, and increases the risk of thrombosis and DIC. Oxygen therapy should be performed under the control of plasma oxidative stress tests. Oxidative stress should be corrected by changing the parameters of oxygen therapy and the use of antioxidants (GSH, vitamins C, A, and E). During oxygen therapy, the blood coagulation state should be constantly tested, paying special

attention to platelet function tests. If necessary, anticoagulants, such as aspirin, clopidogrel, ticagrelor, and heparin, should be used after sepsis diagnostics and during oxygen therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

- Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kivlevan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200-11.
- Rhee C, Jones TM, Hamad Y, Pande A, Varon J, O'Brien C, et al. Prevalence, Underlying causes, and preventability of sepsis-associated mortality in US acute care hospitals. *JAMA Netw Open* 2019;2:e187571.
- Byrne L, Van Haren F. Fluid resuscitation in human sepsis: time to rewrite history? *Ann Intensive Care* 2017;7:4.
- Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019: results from a systematic review and meta-analysis. *Crit Care* 2020;24:239.
- Schlapbach LJ, Kisson N, Alhawsawi A, Aljuaid MH, Daniels R, Gorordo-Delsol LA, et al. World Sepsis Day: a global agenda to target a leading cause of morbidity and mortality. *Am J Physiol Lung Cell Mol Physiol* 2020;319:L518-22.
- Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. *Crit Care Med* 2013;41:1167-74.
- Klastrup V, Hvass AM, Mackenhauer J, Fuursted K, Schønheyder HC, Kirkegaard H, et al. Site of infection and mortality in patients with severe sepsis or septic shock. A cohort study of patients admitted to a Danish general intensive care unit. *Infect Dis (Lond)* 2016;48:726-31.
- Chou EH, Mann S, Hsu TC, Hsu WT, Liu CC, Bhakta T, et al. Incidence, trends, and outcomes of infection sites among hospitalizations of sepsis: a nationwide study. *PLoS One* 2020; 15:e0227752.
- Lever A, Mackenzie I. Sepsis: definition, epidemiology, and di-

- agnosis. *BMJ* 2007;335:879-83.
10. Bewick T, Simmonds M, Chikhani M, Meyer J, Lim WS. Pneumonia in the context of severe sepsis: a significant diagnostic problem. *Eur Respir J* 2008;32:1417-8.
 11. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014;5:4-11.
 12. Szabo BG, Kiss R, Lenart KS, Marosi B, Vad E, Lakatos B, et al. Clinical and microbiological characteristics and outcomes of community-acquired sepsis among adults: a single center, 1-year retrospective observational cohort study from Hungary. *BMC Infect Dis* 2019;19:584.
 13. Vendemiato AV, von Nowakowski A, Marson FA, Levy CE. Microbiological characteristics of sepsis in a University hospital. *BMC Infect Dis* 2015;15:58.
 14. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801-10.
 15. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. *Lancet* 2018;392:75-87.
 16. Weiss SL, Peters MJ, Alhazzani W, Agus M, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020;21:e52-106.
 17. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, Machado FR, et al. Surviving sepsis campaign: research priorities for sepsis and septic shock. *Intensive Care Med* 2018;44:1400-26.
 18. Levy MM, Evans LE, Rhodes A. The Surviving Sepsis Campaign Bundle: 2018 update. *Intensive Care Med* 2018;44:925-8.
 19. Young P, Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, et al. Conservative oxygen therapy for mechanically ventilated adults with sepsis: a post hoc analysis of data from the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). *Intensive Care Med* 2020;46:17-26.
 20. Panditrao MM, Panditrao MM. Optimizing oxygen delivery in sepsis: a review. *Adesh Univ J Med Sci Res* 2019;1(1):8-15.
 21. Heffner JE. The story of oxygen. *Respir Care* 2013;58:18-31.
 22. Shultz SM, Hartmann PM. George E Holtzapple (1862-1946) and oxygen therapy for lobar pneumonia: the first reported case (1887) and a review of the contemporary literature to 1899. *J Med Biogr* 2005;13:201-6.
 23. Ragaller M, Richter T. Acute lung injury and acute respiratory distress syndrome. *J Emerg Trauma Shock* 2010;3:43-51.
 24. Pham T, Rubenfeld GD. Fifty years of research in ARDS. The epidemiology of acute respiratory distress syndrome. A 50th birthday review. *Am J Respir Crit Care Med* 2017;195:860-70.
 25. Taylor MD, Tibby SM. Sometimes more is not always better: ScvO₂ monitoring in pediatric sepsis. *Intensive Care Med* 2020;46:1264-6.
 26. Bouvier NM. Animal models for influenza virus transmission studies: a historical perspective. *Curr Opin Virol* 2015;13:101-8.
 27. Guillon A, Preau S, Aboab J, Azabou E, Jung B, Silva S, et al. Preclinical septic shock research: why we need an animal ICU. *Ann Intensive Care* 2019;9:66.
 28. Bean AG, Baker ML, Stewart CR, Cowled C, Deffrasnes C, Wang LF, et al. Studying immunity to zoonotic diseases in the natural host: keeping it real. *Nat Rev Immunol* 2013;13:851-61.
 29. Zingarelli B, Coopersmith CM, Drechsler S, Efron P, Marshall JC, Moldawer L, et al. Part I: minimum quality threshold in pre-clinical sepsis studies (MQTiPSS) for study design and humane modeling endpoints. *Shock* 2019;51:10-22.
 30. Thom SR, Lauer mann MW, Hart GB. Intermittent hyperbaric oxygen therapy for reduction of mortality in experimental polymicrobial sepsis. *J Infect Dis* 1986;154:504-10.
 31. Guven A, Gundogdu G, Vurucu S, Uysal B, Oztas E, Ozturk H, et al. Medical ozone therapy reduces oxidative stress and intestinal damage in an experimental model of necrotizing enterocolitis in neonatal rats. *J Pediatr Surg* 2009;44:1730-5.
 32. Halbach JL, Prieto JM, Wang AW, Hawisher D, Cauvi DM, Reyes T, et al. Early hyperbaric oxygen therapy improves survival in a model of severe sepsis. *Am J Physiol Regul Integr Comp Physiol* 2019;317:R160-8.
 33. Buras JA, Holt D, Orlow D, Belikoff B, Pavlides S, Reenstra WR. Hyperbaric oxygen protects from sepsis mortality via an interleukin-10-dependent mechanism. *Crit Care Med* 2006;34:2624-9.
 34. Aksenov I, Strauss M, Miller S, Truong C, Hart G. New roles of hyperbaric oxygen in sepsis. *Chest* 2007;132:557A.
 35. Bektas A, Ulusoy M, Mas MR. Do late phase hyperbaric and normobaric oxygen therapies have effect on liver damage? An experimental sepsis model. *Gen Med (Los Angel)* 2019;7:324.
 36. Yamanel L, Kaldirim U, Oztas Y, Coskun O, Poyrazoglu Y, Durusu M, et al. Ozone therapy and hyperbaric oxygen treatment in lung injury in septic rats. *Int J Med Sci* 2011;8:48-55.
 37. Hedetoft M, Garred P, Madsen MB, Hyldegaard O. Hyperbaric oxygen treatment is associated with a decrease in cytokine levels in patients with necrotizing soft-tissue infection. *Physiol Rep* 2021;9:e14757.
 38. Nikitopoulou TS, Papalimperi AH. The inspiring journey of hyperbaric oxygen therapy, from the controversy to the acceptance by the scientific community. *Health Sci J* 2015;9:1.

39. Knighton DR, Halliday B, Hunt TK. Oxygen as an antibiotic. A comparison of the effects of inspired oxygen concentration and antibiotic administration on in vivo bacterial clearance. *Arch Surg* 1986;121:191-5.
40. Bærnthsen NF, Hansen MB, Wahl AM, Simonsen U, Hyldegaard O. Treatment with 24 h-delayed normo- and hyperbaric oxygenation in severe sepsis induced by cecal ligation and puncture in rats. *J Inflamm (Lond)* 2017;14:27.
41. Ozturk A, Yamanel L, Ozenc S, Ince M, Simsek K, Comert B, et al. Comparison of the effects of hyperbaric oxygen and normobaric oxygen on sepsis in rats. *Arch Clin Exp Surg* 2016;5:7-12.
42. Zhang Z, Ji X. Quadratic function between arterial partial oxygen pressure and mortality risk in sepsis patients: an interaction with simplified acute physiology score. *Sci Rep* 2016;6:35133.
43. Calzia E, Asfar P, Hauser B, Matejovic M, Ballestra C, Radermacher P, et al. Hyperoxia may be beneficial. *Crit Care Med* 2010;38(10 Suppl):S559-68.
44. Perner A, De Jong A, Shankar-Hari M. Trials on oxygen supplementation in sepsis: better late than never. *Intensive Care Med* 2020;46:116-8.
45. Muth CM, Radermacher P, Cuzzocrea S. Hyperbaric oxygen and sepsis: time to recognize. *Intensive Care Med* 2005;31:1150-2.
46. Imperatore F, Cuzzocrea S, Luongo C, Liguori G, Scafuro A, De Angelis A, et al. Hyperbaric oxygen therapy prevents vascular derangement during zymosan-induced multiple-organ-failure syndrome. *Intensive Care Med* 2004;30:1175-81.
47. Sakoda M, Ueno S, Kihara K, Arikawa K, Dogomori H, Nuruki K, et al. A potential role of hyperbaric oxygen exposure through intestinal nuclear factor-kappaB. *Crit Care Med* 2004;32:1722-9.
48. Chang KY, Tsai PS, Huang TY, Wang TY, Yang S, Huang CJ. HO-1 mediates the effects of HBO pretreatment against sepsis. *J Surg Res* 2006;136:143-53.
49. Bar-Or D, Carrick MM, Mains CW, Rael LT, Slone D, Brody EN. Sepsis, oxidative stress, and hypoxia: are there clues to better treatment? *Redox Rep* 2015;20:193-7.
50. Chiumello D, Brioni M. Severe hypoxemia: which strategy to choose. *Crit Care* 2016;20:132.
51. Rossi P, Tauzin L, Weiss M, Rostain JC, Sainty JM, Boussuges A. Could hyperoxic ventilation impair oxygen delivery in septic patients? *Clin Physiol Funct Imaging* 2007;27:180-4.
52. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI, et al. Multicenter study of central venous oxygen saturation (ScvO₂) as a predictor of mortality in patients with sepsis. *Ann Emerg Med* 2010;55:40-6.
53. Dahl RM, Grønlykke L, Haase N, Holst LB, Perner A, Wetterslev J, et al. Variability in targeted arterial oxygenation levels in patients with severe sepsis or septic shock. *Acta Anaesthesiol Scand* 2015;59:859-69.
54. Hedenstierna G. Alveolar collapse and closure of airways: regular effects of anaesthesia. *Clin Physiol Funct Imaging* 2003;23:123-9.
55. Stolmeijer R, Bouma HR, Zijlstra JG, Drost-de Klerck AM, Ter Maaten JC, Ligtenberg J. A systematic review of the effects of hyperoxia in acutely ill patients: should we aim for less? *Biomed Res Int* 2018;2018:7841295.
56. Yumoto M, Nakamura F, Katsuya H. Septic shock following hyperbaric oxygen therapy in a patient with ileus. *Jpn Soc Intensive Care Med* 2004;11:127-31.
57. Vincent JL, Taccone FS, He X. Harmful effects of hyperoxia in postcardiac arrest, sepsis, traumatic brain injury, or stroke: the importance of individualized oxygen therapy in critically ill patients. *Can Respir J* 2017;2017:2834956.
58. Page D, Ablordeppey E, Wessman BT, Mohr NM, Trzeciak S, Kollef MH, et al. Emergency department hyperoxia is associated with increased mortality in mechanically ventilated patients: a cohort study. *Crit Care* 2018;22:9.
59. Ni YN, Wang YM, Liang BM, Liang ZA. The effect of hyperoxia on mortality in critically ill patients: a systematic review and meta analysis. *BMC Pulm Med* 2019;19:53.
60. Pannu SR. Too much oxygen: hyperoxia and oxygen management in mechanically ventilated patients. *Semin Respir Crit Care Med* 2016;37:16-22.
61. Damiani E, Donati A, Girardis M. Oxygen in the critically ill: friend or foe? *Curr Opin Anaesthesiol* 2018;31:129-35.
62. Martin DS, Grocott MP. Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Crit Care Med* 2013;41:423-32.
63. Jouffroy R, Saade A, Saint Martin LC, Philippe P, Carli P, Vivien B. Prognosis value of partial arterial oxygen pressure in patients with septic shock subjected to pre-hospital invasive ventilation. *Am J Emerg Med* 2019;37:56-60.
64. Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. *Eurasian J Med* 2017;49:53-8.
65. Garner WL, Downs JB, Reilley TE, Frolicher D, Kargi A, Fabri PJ. The effects of hyperoxia during fulminant sepsis. *Surgery* 1989;105:747-51.
66. Siemieniuk R, Chu DK, Kim LH, Güell-Rous MR, Alhazzani W, Soccia PM, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. *BMJ* 2018;363:k4169.

67. Genga KR, Russell JA. Update of sepsis in the intensive care unit. *J Innate Immun* 2017;9:441-55.
68. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P. Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care* 2015; 5:42.
69. Tuder RM, Hunt JM, Schmidt EP. Hyperoxia and apoptosis. Too much of a good thing? *Am J Respir Crit Care Med* 2011;183:964-5.
70. Rodgers JL, Iyer D, Rodgers LE, Vanthenapalli S, Panguluri SK. Impact of hyperoxia on cardiac pathophysiology. *J Cell Physiol* 2019;234:12595-603.
71. Escobar SJ, Slade JB Jr, Hunt TK, Cianci P. Adjuvant hyperbaric oxygen therapy (HBO2) for treatment of necrotizing fasciitis reduces mortality and amputation rate. *Undersea Hyperb Med* 2005;32:437-43.
72. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2015;2015:CD004123.
73. Chang YH, Chen PL, Tai MC, Chen CH, Lu DW, Chen JT. Hyperbaric oxygen therapy ameliorates the blood-retinal barrier breakdown in diabetic retinopathy. *Clin Exp Ophthalmol* 2006;34:584-9.
74. Piantadosi CA. Carbon monoxide poisoning. *Undersea Hyperb Med* 2004;31:167-77.
75. Minasyan H. Phagocytosis and oxycytosis: two arms of human innate immunity. *Immunol Res* 2018;66:271-80.
76. Minasyan H. Mechanisms and pathways for the clearance of bacteria from blood circulation in health and disease. *Pathophysiology* 2016;23:61-6.
77. Minasyan H. Sepsis and septic shock: Pathogenesis and treatment perspectives. *J Crit Care* 2017;40:229-42.
78. Buico A, Cassino C, Ravera M, Betta PG, Osella D. Oxidative stress and total antioxidant capacity in human plasma. *Redox Rep* 2009;14:125-31.
79. Minasyan H. Sepsis: mechanisms of bacterial injury to the patient. *Scand J Trauma Resusc Emerg Med* 2019;27:19.
80. Krötz F, Sohn HY, Pohl U. Reactive oxygen species: players in the platelet game. *Arterioscler Thromb Vasc Biol* 2004;24:1988-96.
81. Yun SH, Sim EH, Goh RY, Park JI, Han JY. Platelet activation: the mechanisms and potential biomarkers. *Biomed Res Int* 2016;2016:9060143.
82. Iuliano L, Colavita AR, Leo R, Praticò D, Violi F. Oxygen free radicals and platelet activation. *Free Radic Biol Med* 1997;22:999-1006.
83. Qiao J, Arthur JF, Gardiner EE, Andrews RK, Zeng L, Xu K. Regulation of platelet activation and thrombus formation by reactive oxygen species. *Redox Biol* 2018;14:126-30.
84. Wachowicz B, Olas B, Zbikowska HM, Buczy ski A. Generation of reactive oxygen species in blood platelets. *Platelets* 2002;13:175-82.
85. Sill JC, Proper JA, Johnson ME, Uhl CB, Katusic ZS. Reactive oxygen species and human platelet GP IIb/IIIa receptor activation. *Platelets* 2007;18:613-9.
86. Helms CC, Marvel M, Zhao W, Stahle M, Vest R, Kato GJ, et al. Mechanisms of hemolysis-associated platelet activation. *J Thromb Haemost* 2013;11:2148-54.
87. Davis RP, Miller-Dorey S, Jenne CN. Platelets and coagulation in infection. *Clin Transl Immunology* 2016;5:e89.
88. Gawaz M, Fateh-Moghadam S, Pilz G, Gurland HJ, Werdan K. Platelet activation and interaction with leucocytes in patients with sepsis or multiple organ failure. *Eur J Clin Invest* 1995;25:843-51.
89. Alhamdi Y, Toh CH. Recent advances in pathophysiology of disseminated intravascular coagulation: the role of circulating histones and neutrophil extracellular traps. *F1000Res* 2017;6:2143.
90. Carrim N, Arthur JF, Hamilton JR, Gardiner EE, Andrews RK, Moran N, et al. Thrombin-induced reactive oxygen species generation in platelets: a novel role for protease-activated receptor 4 and GPIIb. *Redox Biol* 2015;6:640-7.
91. Kambas K, Mitroulis I, Ritis K. The emerging role of neutrophils in thrombosis—the journey of TF through NETs. *Front Immunol* 2012;3:385.
92. Delabranche X, Boisramé-Helms J, Asfar P, Berger A, Mootien Y, Lavigne T, et al. Microparticles are new biomarkers of septic shock-induced disseminated intravascular coagulopathy. *Intensive Care Med* 2013;39:1695-703.
93. Morrissey JH. Polyphosphate: a link between platelets, coagulation and inflammation. *Int J Hematol* 2012;95:346-52.
94. Arman M, Krauel K, Tilley DO, Weber C, Cox D, Greinacher A, et al. Amplification of bacteria-induced platelet activation is triggered by FcγRIIA, integrin αIIbβ3, and platelet factor 4. *Blood* 2014;123:3166-74.
95. Antoniak S. The coagulation system in host defense. *Res Pract ThrombHaemost* 2018;2:549-57.
96. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. *Thromb Res* 2012;129:290-5.
97. Broaddus VC. Murray and Nadel's textbook of respiratory medicine. 6th ed. Philadelphia (PA): Elsevier Saunders; 2016.
98. Hafen B, Sharma S. Oxygen saturation [Internet]. StatPearls.

- 2021;[cited 2021 Dec 10]. Available from: <https://www.statpearls.com/kb/viewarticle/26491>.
99. Weibel ER. The pathway for oxygen. Cambridge, Harvard University Press. 1984.
 100. Pittman RN. Oxygen transport. San Rafael (CA), Morgan and Claypool Life Sciences. 2011;[cited 2021 Dec 1]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK54103/>.
 101. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: the haemoglobin-oxygen dissociation curve. *Breathe (Sheff)* 2015;11:194-201.
 102. Christmas KM, Bassingthwaighe JB. Equations for O₂ and CO₂ solubilities in saline and plasma: combining temperature and density dependences. *J Appl Physiol* (1985) 2017;122:1313-20.
 103. Wojciechowski WV. Respiratory care sciences: an integrated approach. Clifton Park (NY), Delmar Cengage Learning. 2014.
 104. Beachey W. Respiratory care anatomy and physiology: Foundations for Clinical Practice. St. Louis (MO), Elsevier. 2018.
 105. Biolo G, Antonione R, De Cicco M. Glutathione metabolism in sepsis. *Crit Care Med* 2007;35(9 Suppl):S591-5.
 106. Kim JS, Kwon WY, Suh GJ, Kim KS, Jung YS, Kim SH, et al. Plasma glutathione reductase activity and prognosis of septic shock. *J Surg Res* 2016;200:298-307.
 107. Gamarra Y, Santiago FC, Molina-López J, Castaño J, Herrera-Quintana L, Domínguez Á, et al. Pyroglutamic acidosis by glutathione regeneration blockage in critical patients with septic shock. *Crit Care* 2019;23:162.
 108. Flåring U, Wernerman J. Glutathione in sepsis and multiple organ failure. In: Vincent JL. In: Yearbook of intensive care and emergency medicine. Berlin, Heidelberg, Springer. 2008, pp 444-53.
 109. Pravda J. Metabolic theory of septic shock. *World J Crit Care Med* 2014;3:45-54.
 110. Madian AG, Regnier FE. Proteomic identification of carbon-ylated proteins and their oxidation sites. *J Proteome Res* 2010; 9:3766-80.
 111. Weber D, Davies MJ, Grune T. Determination of protein carbonyls in plasma, cell extracts, tissue homogenates, isolated proteins: focus on sample preparation and derivatization conditions. *Redox Biol* 2015;5:367-80.
 112. Kuhn SO, Meissner K, Mayes LM, Bartels K. Vitamin C in sepsis. *Curr Opin Anaesthesiol* 2018;31:55-60.
 113. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, Shaw GM. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. *Crit Care* 2017;21:300.
 114. Pakala R, Waksman R. Currently available methods for platelet function analysis: advantages and disadvantages. *Cardiovasc Revasc Med* 2011;12:312-22.
 115. Layios N, Delierneux C, Hego A, Huart J, Gosset C, Lecut C, et al. Sepsis prediction in critically ill patients by platelet activation markers on ICU admission: a prospective pilot study. *Intensive Care Med Exp* 2017;5:32.
 116. Zhou L, Schmaier AH. Platelet aggregation testing in platelet-rich plasma: description of procedures with the aim to develop standards in the field. *Am J Clin Pathol* 2005;123:172-83.
 117. Collet JP, Montalescot G. Platelet function testing and implications for clinical practice. *J Cardiovasc Pharmacol Ther* 2009;14:157-69.
 118. Paniccia R, Priora R, Liotta AA, Abbate R. Platelet function tests: a comparative review. *Vasc Health Risk Manag* 2015;11:133-48.
 119. Darling CE, Sala Mercado JA, Quiroga-Castro W, Tecco GF, Zelaya FR, Conci EC, et al. Point-of-care assessment of platelet reactivity in the emergency department may facilitate rapid rule-out of acute coronary syndromes: a prospective cohort pilot feasibility study. *BMJ Open* 2014;4:e003883.
 120. Fowler AA 3rd, Syed AA, Knowlson S, Sculthorpe R, Farthing D, DeWilde C, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. *J Transl Med* 2014;12:32.
 121. Zabet MH, Mohammadi M, Ramezani M, Khalili H. Effect of high-dose Ascorbic acid on vasopressor's requirement in septic shock. *J Res Pharm Pract* 2016;5:94-100.
 122. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. *Chest* 2017;151:1229-38.
 123. Fowler AA 3rd, Truitt JD, Hite RD, Morris PE, DeWilde C, Priddy A, et al. Effect of vitamin C infusion on organ failure and biomarkers of inflammation and vascular injury in patients with sepsis and severe acute respiratory failure: the CLTRIS-ALI randomized clinical trial. *JAMA* 2019;322:1261-70.
 124. Kalil AC. Lack of benefit of high-dose vitamin c, thiamine, and hydrocortisone combination for patients with sepsis. *JAMA* 2020;323:419-20.
 125. de Grooth HJ, Manubulu-Choo WP, Zandvliet AS, Spoelstra-de Man A, Girbes AR, Swart EL, et al. Vitamin C pharmacokinetics in critically ill patients: a randomized trial of four IV regimens. *Chest* 2018;153:1368-77.
 126. Wang Y, Lin H, Lin BW, Lin JD. Effects of different ascorbic acid

- doses on the mortality of critically ill patients: a meta-analysis. *Ann Intensive Care* 2019;9:58.
127. Spoelstra-de Man A, Oudemans-van Straaten HM, Berger MM. Adjuvant vitamin C for sepsis: mono or triple? *Crit Care* 2019;23:425.
 128. Kashiouris MG, L'Heureux M, Cable CA, Fisher BJ, Leichtle SW, Fowler AA. The emerging role of vitamin C as a treatment for sepsis. *Nutrients* 2020;12:292.
 129. Ribeiro Nogueira C, Ramalho A, Lameu E, Da Silva Franca CA, David C, Accioly E. Serum concentrations of vitamin A and oxidative stress in critically ill patients with sepsis. *Nutr Hosp* 2009;24:312-7.
 130. Zhang X, Yang K, Chen L, Liao X, Deng L, Chen S, et al. Vitamin A deficiency in critically ill children with sepsis. *Crit Care* 2019;23:267.
 131. Cherukuri L, Gewirtz G, Osea K, Tayek JA. Vitamin A treatment for severe sepsis in humans; a prospective randomized double blind placebo-controlled clinical trial. *Clin Nutr ESPEN* 2019;29:49-51.
 132. Hariri Ahari M, Pishbin E. Vitamin D and sepsis. *Int Sch Res Notices* 2014;1:225-8.
 133. Behera CK, Sahoo JP, Patra SD, Jena PK. Is lower vitamin D level associated with increased risk of neonatal sepsis? a prospective cohort study. *Indian J Pediatr* 2020;87:427-32.
 134. Kempker JA, Han JE, Tangpricha V, Ziegler TR, Martin GS. Vitamin D and sepsis: an emerging relationship. *Dermatoendocrinol* 2012;4:101-8.
 135. Kempker JA, Martin GS. Vitamin D and sepsis: from associations to causal connections. *Inflamm Allergy Drug Targets* 2013;12:246-52.
 136. Shojaei M, Sabzegahabaei A, Valaei Barhagh H, Soltani S. The correlation between serum level of vitamin D and outcome of sepsis patients: a cross-sectional study. *Arch Acad Emerg Med* 2019;7:e1.
 137. Amrein K, Sourij H, Wagner G, Holl A, Pieber TR, Smolle KH, et al. Short-term effects of high-dose oral vitamin D3 in critically ill vitamin D deficient patients: a randomized, double-blind, placebo-controlled pilot study. *Crit Care* 2011;15:R104.
 138. Minter BE, Lowes DA, Webster NR, Galley HF. Differential effects of MitoVitE, α -tocopherol and trolox on oxidative stress, mitochondrial function and inflammatory signalling pathways in endothelial cells cultured under conditions mimicking sepsis. *Antioxidants (Basel)* 2020;9:195.
 139. Yamakawa K, Umemura Y, Murao S, Hayakawa M, Fujimi S. Optimal timing and early intervention with anticoagulant therapy for sepsis-induced disseminated intravascular coagulation. *Clin Appl Thromb Hemost* 2019;25:1076029619835055.
 140. Umemura Y, Yamakawa K, Hayakawa M, Hamasaki T, Fujimi S, Japan Septic Disseminated Intravascular Coagulation (J-Septic DIC) study group. Screening itself for disseminated intravascular coagulation may reduce mortality in sepsis: a nationwide multicenter registry in Japan. *Thromb Res* 2018;161:60-6.
 141. Laursen MA, Larsen JB, Hvas AM. Platelet function in disseminated intravascular coagulation: a systematic review. *Platelets* 2018;29:238-48.
 142. Assinger A, Schrottmaier WC, Salzman M, Rayes J. Platelets in sepsis: an update on experimental models and clinical data. *Front Immunol* 2019;10:1687.
 143. Kudo D, Hayakawa M, Iijima H, Yamakawa K, Saito S, Uchino S, et al. The treatment intensity of anticoagulant therapy for patients with sepsis-induced disseminated intravascular coagulation and outcomes: a multicenter cohort study. *Clin Appl Thromb Hemost* 2019;25:1076029619839154.
 144. Dewitte A, Lepreux S, Villeneuve J, Rigotherier C, Combe C, Ouattara A, et al. Blood platelets and sepsis pathophysiology: a new therapeutic prospect in critically [corrected] ill patients? *Ann Intensive Care* 2017;7:115.
 145. Lösche W, Boettel J, Kabisch B, Winning J, Claus RA, Bauer M. Do aspirin and other antiplatelet drugs reduce the mortality in critically ill patients? *Thrombosis* 2012;2012:720254.
 146. Winning J, Neumann J, Kohl M, Claus RA, Reinhart K, Bauer M, et al. Antiplatelet drugs and outcome in mixed admissions to an intensive care unit. *Crit Care Med* 2010;38:32-7.
 147. Kelm DJ, Valerio-Rojas JC, Cabello-Garza J, Gajic O, Cartin-Ceba R. Predictors of disseminated intravascular coagulation in patients with septic shock. *Int Sch Res Notices* 2013;219048.
 148. Tsao CM, Ho ST, Wu CC. Coagulation abnormalities in sepsis. *Acta Anaesthesiol Taiwan* 2015;53:16-22.
 149. Jennings LK. Mechanisms of platelet activation: need for new strategies to protect against platelet-mediated atherothrombosis. *ThrombHaemost* 2009;102:248-57.
 150. Ouyang Y, Wang Y, Liu B, Ma X, Ding R. Effects of antiplatelet therapy on the mortality rate of patients with sepsis: a meta-analysis. *J Crit Care* 2019;50:162-168.
 151. Wang Y, Ouyang Y, Liu B, Ma X, Ding R. Platelet activation and antiplatelet therapy in sepsis: a narrative review. *Thromb Res* 2018;166:28-36.
 152. Senno SL, Pechet L, Bick RL. Disseminated intravascular coagulopathy (DIC): pathophysiology, laboratory diagnosis, and management. *J Intensive Care Med* 2000;15:144-58.
 153. Sossdorf M, Otto GP, Boettel J, Winning J, Lösche W. Benefit of

- low-dose aspirin and non-steroidal anti-inflammatory drugs in septic patients. *Crit Care* 2013;17:402.
154. Eisen DP, Reid D, McBryde ES. Acetyl salicylic acid usage and mortality in critically ill patients with the systemic inflammatory response syndrome and sepsis. *Crit Care Med* 2012;40:1761-7.
155. Eisen DP. Manifold beneficial effects of acetyl salicylic acid and nonsteroidal anti-inflammatory drugs on sepsis. *Intensive Care Med* 2012;38:1249-57.
156. Otto GP, Sossdorf M, Boettel J, Kabisch B, Breuel H, Winning J, et al. Effects of low-dose acetylsalicylic acid and atherosclerotic vascular diseases on the outcome in patients with severe sepsis or septic shock. *Platelets* 2013;24:480-5.
157. Eisen DP, Leder K, Woods RL, Lockery JE, McGuinness SL, Wolfe R, et al. Effect of aspirin on deaths associated with sepsis in healthy older people (ANTISEPSIS): a randomised, double-blind, placebo-controlled primary prevention trial. *Lancet Respir Med* 2021;9:186-95.
158. Evangelista V, Manarini S, Dell'Elba G, Martelli N, Napoleone E, Di Santo A, et al. Clopidogrel inhibits platelet-leukocyte adhesion and platelet-dependent leukocyte activation. *ThrombHaemost* 2005;94:568-77.
159. Winning J, Reichel J, Eisenhut Y, Hamacher J, Kohl M, Deigner HP, et al. Anti-platelet drugs and outcome in severe infection: clinical impact and underlying mechanisms. *Platelets* 2009;20:50-7.
160. Dobesh PP, Oestreich JH. Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety. *Pharmacotherapy* 2014;34:1077-90.
161. Storey RE, James SK, Siegbahn A, Varenhorst C, Held C, Ycas J, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. *Platelets* 2014;25:517-25.
162. Scully M, Levi M. How we manage haemostasis during sepsis. *Br J Haematol* 2019;185:209-218.
163. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of action and pharmacology of unfractionated heparin. *Arterioscler Thromb Vasc Biol* 2001;21:1094-6.
164. Liu XL, Wang XZ, Liu XX, Hao D, Jaladat Y, Lu F, et al. Low-dose heparin as treatment for early disseminated intravascular coagulation during sepsis: a prospective clinical study. *Exp Ther Med* 2014;7:604-8.
165. Polderman KH, Girbes AR. Drug intervention trials in sepsis: divergent results. *Lancet* 2004;363:1721-3.
166. Iba T, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. *Anesthesiology* 2020;132:1238-45.
167. Wang C, Chi C, Guo L, Wang X, Guo L, Sun J, et al. Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systematic review and meta-analysis. *Crit Care* 2014;18:563.